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Abstract:

The invention relates to therapeutic agents containing anionic oxygen radicals and/or their secondary or decomposition products and their use in combination with analgesics in relieving pain

Specification:

Object

[0001] The invention relates to of oxygen anion radicals (superoxide radical, abbreviated in the following with "SAR" or "superoxide", O2< - >) and/or their following and degradation products (z. B. H2O2, O2H or their hydrate cluster) contained therapeutic agents and their use in combination with analgesics to the treatment of pains.

State of the art

[0002] The therapeutic use of air ions is known. So far experiences are appropriate for Traitement de l'asthme bronchique par l'a ro - ionization negative to the therapeutic application of air ions major with the bronchial asthma and with chronic obstructive lung illnesses before Boulatov P.K., (1975). In: Rager, OD., problem d'ionization et d'a ro. Paris, Maloine, 178-85). In addition, there are reports over its successful application with combustions, with the shock syndrome, with rheumatoid arthritis, with chronic pain syndromes, the particular migraine, with essential hypertension, with depressive states and the ulcer (Tchijevsky A.L., (1960), [Aeroionization in national economy.], 758 FF., Moskow, Publishing House OF the State Planing Commision OF the USSR).
[0003] The therapeutic agents used in the pain treatment can be divided into opiodartige and not opiodartige analgesics. In particular to the treatment from potent and chronic pains frequent Opioide becomes and/or. Morphine derivatives used. One is endeavored because of the serious side effects, the indication area for Morphiate on as small a group of patients as possible (z. B. Fresh-operated to limit Schwerstverbrannte or cancer patient the final stage of their disease). From these reasons in particular potent analgesics come only very zögerlich to the use with younger persons, which have to suffer bottom potent pains.
[0004] A significant drawback of these analgesics exists in the known, partially very severe side effects such as z. B. Breath depression, nausea and vomiting, spasms of various organs (cerebral, bronchial and. A.), mental confusion as well as and. A. renaler toxischer Effekte. Beyond that the risk of a medicine

dependence is not to be excluded with a longer ingestion of these analgesics.
[0005] It is known that negative air ions have an influence on the effect of morphine (Beardwood, C. J. and Jordi, P. M., (1990). Effect OF negative air of ion on morphine induced CHANGEs into the latency OF the tail repair reflex. Bioelectromagnetics (N.Y.) 11 (3), 207-212). In this publication is described that with rats, which negative air ions were exposed the effect is waived on the tail twitching reflex by morphine.
[0006] The known sources of literature and experiences in the therapeutic application of negative air ions exhibit contradictions and ambiguity, which so far in substantial circumference the practical use of the air ion therapy hindered. One of the main causes for the contradictory findings lies in the construction and use of unselektiven and inappropriate ionizer for a therapeutic application. During the use of these inhalers arises besides a loss at physiological important oxygen anion radicals (SAR) on the path to the effect place. It becomes therefore a non specific mixture of negative gas ions with if necessary low content at oxygen anion radicals administered.
[0007] With that the instant invention underlying term of the "oxygen anion radicals and their following or degradation products" in particular the radicals are and/or. Radikalbildner O2< - > , H2O2, O2H or their hydrate cluster meant, which exhibit according to invention a physiological effect similar in the sense.
[0008] By an apparatus, how them are for example in the Patent Laid open DE 41 12 459 A1 described, oxygen anion radicals become generated. Alternative one to the physical formation of oxygen anion radicals (DE 41 42 459 A1) is also their chemical and/or. enzymatic generation possible (Fridovich, I., (1970), "quantitative ones aspects OF the production OF of superoxides anion radical by milk xanthine oxidase." J. Biol. Chem. one. 245, 4053).

Object

[0009] The instant invention is the basis the object to increase the efficacy from analgesics to so that the dosage normally conventional for pain treatment can become significantly reduced.
[0010] Due to the variety of individual parameters during the pain treatment (individual Pharmakokinetik of the analgesic, a pain cause, individual pain feeling, etc.) precise indications can conventional" dosage of an analgesic be normally met to that "preferably on the basis comparison values, which at an individual obtained became.
[0011] Those advantages which can be obtained exist particularly in a reduction of the not insignificant risks of side effects and medicine dependence.
[0012] The object becomes according to invention by the combined use of oxygen anion radicals and/or their degradation products and an analgesic dissolved. Here the oxygen anion radicals become generated selective with the administration in a suitable device due to their metastable state more immediate forwards or simultaneous (see. z. B. DE 41 12 459 A1).
[0013] The other also the application of liposomes is conceivable, which serve as carriers for enzymes (z. B. Xanthinoxidase, Flavin depends dehydrogenases etc.) and in this way oxygen anion radicals exclusive at the target location generate.

[0014] The application of the oxygen anion radicals made preferably low-loss by inhalation or intranasal application. The time is preferably present and/or during the administration of an analgesic. Alternative one is however also an alternate interval therapy of SAR and analgesic suitable, whereby the oxygen anion radicals with a Bildungsgeschwindigkeit of 100 pmol 1< - 1> s< - 1> to 1 fmol 1< - 1> s< - 1> the order provided become. The analgesic can become in the conventional in each case manner administered.
[0015] The novel effect, which is the basis the instant invention, exists in a synergistic antinozizeptiven effect of oxygen anion radicals and/or its following or degradation products and the applied analgesic, so that the dose required to the achievement of a defined effect can become around at least 50% reduced.
[0016] In order to reach the synergetic effect according to invention, for example the subsequent analgesics are suitable: Morphines, morphine derivatives and morphine analogues, other Narkoanalgetika, analgesics of vegetable origin, not opioidartige analgesics such as z. B. 3,5 - Pyrazolinonderivate, Paracetamol, 3,5-Pyrazolidindionderivate, Salicylsäurederivate, Anthranilsäurederivate, aryl acetic acid derivatives, Arylpropionsäurederivate, Azapropazon, piroxicam, Tenoxicam. Likewise more conceivable the use of the oxygen anion radicals is in combination with Sedativa as for example bar bit urates, Methaqualon, Chloralhydrat, benzodiazepines, Doxylaminsuccinat, Diphenhydramin and. A.
[0017] Surprising one was now found that the use according to invention of oxygen anion radicals shows significant synergistic antinozizeptive effects in combination with analgesics.
[0018] This is the surprising regarding the publication in Bioelectromagnetics (N.Y.) 11 (3), 207-212, 1990, described in which an attenuation of the effect of morphine is by negative air ions.
[0019] Impressive effects the shown Verabreichtung of oxygen anion radicals or H2O2 in animal experimentally supported pain investigations. With the animal experimental treatment of potent pains (3. Step from 3 to Melzack, special edition, "Morphium and severe chronic pains", Spektrum der Wissenschaft, 1991) is with application of the agent according to invention only approx. 1/20 of the Morphiumderivat dose of a comparable pain suppression necessary.
[0020] Already a reduction of the therapeutic required dose around 50 percent represents an enormous advance of the state of the art, since thereby potential side effects become greatly reduced.
[0021] For the animal experimental examination of the pain-inhibitive effect of a medicine various methods stand to the selection, which is the person skilled in the art known.
[0022] In the subsequent listed examples the test of pain sensitivity became performed after Randall Selitto with a Analgesimeter. Here the intensity of the critical pressure (IKD) became certain, which a plastic cone must exercise on the Hinterpfote of a rat, until the animal withdraws its paw. The results of the subsequent studies become in relative scale units of the apparatus indicated, a relative scale unit correspond to a pressure increase around 20 G.
[0023] First the basal line of the IKD became by 3 measurements in intervals of 5-10 min and averaging certain with each animal. In the other course of the

experiment, after the bottom smoldering leagues became cans of the analgesics determined, pain sensitivity became over a period of 3 to 3.5 hours in 30 min intervals measured. The first measurements made 30 min after application of the antinozizeptiven substances.
[0024] As other test system the permanent chemical attraction served after Melzack. Here the experimental animal immediate before the application of the analgesic became a 3,5%ige formaldehyde solution into the anterior paw injected and the subsequent period certain, until the animal set this paw the bottom.
[0025] According to Melzack (special edition, "Morphium and severe chronic pains", Spektrum der Wissenschaft, 1991) one differentiates two various neuronal systems for the pain sensation, the medial system for the chronic pain (tonischer pain) and the lateral system, which are responsible for acute pain (phasischer pain). The study of the antinozizeptiven effect with chronic pains became used therefore the hurting procedure for the determination of tonischer pains (formaldehyde test after Melzack and test after edge all Selitto).
[0026] One points out that during the test with all experimental animals a characteristic reduction of the IKD in the sense of a sensitization of the pain sensation was to be observed and with the statistical evaluation of the data corresponding considered became.
[0027] The proportional increase of the IKD, by which the analgesic effect can become quantified, became calculated according to the subsequent formula:
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whereby IKDexp, o and IKDk, o designate the initial values of the IKD in the attempt and control group and IKDexp, i and IKDk, i the IKD values of the two groups to the time i.
[0028] Die unterschwellige Dosis der zu untersuchenden Analgetika wurde zu Beginn der Tests ermittelt; the method is exemplary listed for Trimeperimidin (1 mg/kg) (example 1). In analogous manner bottom-smolder-lies dose from Metamizol sodium became to 30 mg/kg as well as from morphine to 0.5 mg/kg the body weight certain. With the bottom smoldering leagues cans of the analgesics the synergetic effect became by the SAR in the subsequent examples 1 to 7 tested.
[0029] The inhalation of oxygen anion radicals strengthens the significant analgetische efficacy of morphine just like those of the narkotischen analgesic Trimeperimidin, the analogue of the Phenyl n Methylpethydin part of the morphine (z. B. Pethidin). This synergetic effect adjusts itself both immediate after a 50minütigen inhalation of the oxygen anion radicals and after course of 2 hours after the inhalation. Here in each case bottom-smolder-lie cans of the analgesics became used. As test models the Randall Selitto test (example 2 and 7) served.
[0030] The inhalation of oxygen anion radicals strengthens the analgesic effect of the not opioidartigen analgesic just like the intranasal administration of H_2O_2 sodium Noraminopyrin methansulfonat (syn. Metamizol). The strengthening effect developed itself more immediate after the inhalation and at bottom smoldering leagues cans of the analgesic. As test model likewise the Randall Selitto test (examples 3 and 6) served.

[0031] The inhalation of oxygen anion radicals strengthens the analgesic effect of the morphinhaltigen narkotischen analgesic Papaveretrum, which exhibits the subsequent composition just like the intranasal administration of H2O2: 48-50% of the morphine, 29.9-34.2% of other Opium Alkoloiden and approx. 15% of the Vasodilators Papaverin. The synergetic effect became with lowered cans of the analgesic (approx. 20% of the normal dose) achieved. As test model the permanent chemical attraction served after Melzack (example 8).

Aufürungsbeispiel

[0032] The subsequent examples describe the invention. The magnitude of the experimental groups amounted to in each case 10 animals, if not differently mentioned.

Example 1: Determination of the bottom smoldering leagues dose of Trimeperimidin (Fig. 1)
[0033] 3 various dosages of the analgesic Trimeperimidin in a test became after Randall Selitto investigated:
5 mg/kg, 2 mg/kg and 1 mg/kg. The analgesic became white rats in a volume of 0,2 ml intraperitoneal applied, the white rats of the control group became water injected.
[0034] With a dose of 5 mg/kg a maximal change of the IKD became 30 minutes after the application of the analgesic observed, the value increased by 72% opposite the basal IKD and by 96% opposite the control group. Significant differences existed over a period of 90 minutes.
[0035] With a dose of 2 mg/kg a maximal change of the IKD became likewise 30 minutes after the application of the analgesic observed, the value increased by 27% opposite the basal IKD and by 75% opposite the control group. Significant differences existed over a period of 120 minutes.
[0036] With a dose of 1 mg/kg no significant changes of the IKD could become opposite the basal value and the control group observed. This bottom-smolderlies to dose became with the other experiments used.

Example 2: Synergetic effect of oxygen anion radicals and PROM DOL (Fig. 2)
[0037] The subsequent experimental groups in a test became after Randall Selitto investigated:

1. [Control] without inhalation, application of water
2. [Trimeperimidin] without inhalation, application of Trimeperimidin
3. [SAR] with inhalation, application of water
4. [SAR+Trimeperimidin] with inhalation, application of Trimeperimidin

[0038] After the determination of the basalIKD the animals of the 3 became. and 4. Experimental group for the durations of 50 minutes in an atmosphere with oxygen anion radicals maintained (1 pmol s< - 1>), afterwards PROM DOL in bottom smoldering leagues a dose (1 mg/kg) or distilled water injected became. The results are in Fig. 2 shown and show 30 minutes after the application of the analgesic for the 4. Experimental group a significant increase of the IKD around 29% ($p < 0.05$), after 90 minutes around 24% ($p < 0.05$) and after 150 minutes around 54% ($p < 0.01$) in the comparison to the 3. Experimental group. In the

comparison to 2. Experimental group amounted to the significant magnification of the IKD value after 120 and 150 minutes 42% (p< 0.05) and 88% (p< 0.01). Significant differences existed over a period of over 180 minutes.

Example 3: Synergetic effect of oxygen anion radicals and Metamizol sodium (Fig. 3)
[0039] The subsequent experimental groups in a test became after Randall Selitto investigated:

1. [Control] without inhalation, application of water
2. [Metamizol] without inhalation, application of Metamizol
3. [SAR] with inhalation, application of water
4. [SAR+Metamizol] with inhalation, application of Metamizol

[0040] After the determination of the basalIKD the animals of the 3 became. and 4. Experimental group for the durations of 50 minutes in an atmosphere with oxygen anion radicals maintained (1 pmol s< - 1>), afterwards Metamizol in bottom smoldering leagues a dose (30 mg/kg) or distilled water injected became. The results are in Fig. 3 shown and shows 150 minutes after the application of the analgesic for the 4. Experimental group a significant increase of the IKD around 64% (p< 0.01) in the comparison to the 3. Group. In the comparison to [Metamizol] - group amounted to the magnification of the IKD value after 150 minutes 61% (p< 0.01), after 180 minutes 89% (p< 0.01) and after 210 minutes 83% (p< 0.01). Signifikante Unterschiede bestanden nur in der späten Phase, d. h. late as 120 minutes after the application of the analgesic.

Example 4: Synergetic effect of oxygen anion radicals and 2 hours delayed application of Trimeperimidin (Fig. 4)
[0041] The subsequent experimental groups in a test became after Randall Selitto investigated:

1. [SAR] with inhalation, application of water
2. [SAR+Trimeperimidin] with inhalation, application of Trimeperimidin

[0042] After the determination of the basalIKD the animals of the two experimental groups for the durations of 50 minutes in an atmosphere with oxygen anion radicals became maintained (1 pmol s< - 1>), only 2 hours latter PROM DOL in bottom smoldering leagues a dose (1 mg/kg) or distilled water applied became. The results are in Fig. 4 shown. In the comparison to the 1. Experimental group amounted to the magnification of the IKD value after 150 minutes 35% (p< 0.05) and after 180 minutes 46% (p< 0.05). Significant differences existed in a late phase, D. h. approx. 150 minutes after applications of the analgesic.

Example 5: Influence of Nialamid on the synergetic effect of SAR and Trimeperimidin (Fig. 5)
[0043] The subsequent experimental groups in a test became after Randall Selitto investigated:

1. [Nialamid+Superoxid+Trimeperimidin] with inhalation, application of Nialamid and Trimeperimidin

2. [Nialamid+Superoxid] with inhalation, application of Nialamid
3. [Superoxid+Trimeperimidin] with inhalation, application of Trimeperimidin
4. [Superoxide] with inhalation, application of water

[0044] After the determination of the basalIKD the animals of the 1 received. and 2. Experimental group intraperitoneal Nialamid (1 mg/kg in 0,2 ml aqueous solution), the other rats received 0.2 ml waters. An hour, after the effect of the Mao inhibitor had Nialamid used, the animals 50 minutes prolonged in an atmosphere with oxygen anion radicals maintained (1 became latter pmol s< -1>) and soon after PROM DOL in bottom smoldering leagues a dose (1 mg/kg) or distilled water applied. The results are in Fig. 5 shown. The 2. and 4. Group shown during the entire measuring period a relative stable level of the IKD. 3. Group a shown biphasischen analgetischen effect, while could become only the later of the two analgetischen phases blocked in the first experimental group by the application of Nialamid selective.

Example 6: Synergetic effects of H2O2 and Metamizol sodium or Trimeperimidin (Fig. 6)
[0045] The subsequent experimental groups in a test became after Randall Selitto investigated:

1. [Control] intranasal application of H2O, after 15 minutes intraperitoneal injection of H2O
2. [Peroxide] intranasal application of H2O2, after 15 minutes intraperitoneal injection of H2O
3. [Peroxid+Trimeperimidin] intranasal application of H2O2, after 15 minutes intraperitoneal injection of Trimeperimidin
4. [Peroxid+Metamizol] intranasal application of H2O2, after 15 minutes intraperitoneal injection of Metamizol sodium

[0046] After the determination of the basalIKD the animals water became and/or. H2O2 (50 l, 10 oil) intranasal applied and after 15 minutes the respective analgesic in its bottom smoldering leagues dose or distilled water applied. The results are in Fig. 6 shown, the 1. and 2. Group shown in the course of the IKD no differences. While 3. Experimental group (H2O2 and Trimeperimidin) significant synergetic effect shown, could not in the 4. Experimental group already after 30 minutes a significant increase of the IKD around 37% ($p < 0.05$) in the comparison to the control group found becomes. In the comparison to [peroxide] - group amounted to the magnification of the IKD value after 90 minutes 43% ($p < 0.05$).

Example 7: Synergetic effect of oxygen anion radicals and morphine (Fig. 7)
[0047] The subsequent experimental groups in a test became after Randall Selitto investigated:

1. [Control] without inhalation, application of water
2. [Morphine] without inhalation, application of morphine
3. [SAR] with inhalation, application of water
4. [SAR+Morphin] with inhalation, application of morphine
5. [Naloxon] without inhalation, application of Naloxon and waters

6. [Naloxon+Morphin] without inhalation, application of Naloxon and morphine
7. [Naloxon+SAR] with inhalation, application of Naloxon and waters
8. [Naloxon+SAR+Morphin] with inhalation, application of Naloxon and morphine

[0048] After the determination of the basalIKD the animals of the 3 became. , 4. , 7. und 8. Experimental group for the durations of 50 minutes in an atmosphere with oxygen anion radicals maintained (1 pmol s< - 1>), immediately after it became, the experimental groups specified above corresponding, morphine in bottom smoldering leagues a dose (0.5 mg/kg) or distilled water applied. Naloxon became already 15 minutes before the inhalation in a dose of 0,5 mg/kg administered. The critical pressure became 30, 60, 120 and 180 minutes after the morphine injection measured. The recovered results are in the tables 1 and 2 listed as well as in Fig. 7A and 7B graphic shown. [image - lake original document] [image - lake original document]

Example 8: Determination of the continuous pain white rats
[0049] The subsequent experimental groups in a test became after Melzack investigated:
1. [Control] without analgesic
2. [Omnopon] intraperitoneal injection of Omnopon
3. [Superoxid+Omnopon] inhalation of superoxide and intraperitoneal injection of Omnopon
4. [H2O2+Omnopon] intranasal application of H2O2 and intraperitoneal injection of Omnopon

Number of the animals:
[Control] = 16
[Omnopon] = 7
[Superoxide + Omnopon] = 9
[H2O2 = Omnopon] = 7

[0050] The experimental animals of all groups first 100 l of a 3,5%igen formaldehyde solution (in 0,9%iger NaCl solution) became subcutaneous injected into the anterior paw.
[0051] Omnopon became the animals of the group 2-4 in for this pain model upper smoldering leagues dose of 0,1 mg/kg in physiological saline intraperitoneal and within a minute after injection of the formaldehyde solution applied. The application of the oxygen anion radicals (group 3) made by inhalation for a period of 45-60 minutes in a distance 5-10 cms of the ionization electrode and already before the injection of the formaldehyde solution. The animals of the group 4 in each case 50 l 10 mol of a hydrogen peroxide solution became (with 0,9% common salt) as well as the formaldehyde and Omnopon solution within a minute in each nasal cavity administered.
[0052] By the time of the formaldehyde injection the period became certain on, until the rats replaced the affected anterior paw for the first time for ground contact.
[0053] With the animals of the group 1 (control without analgesic) this value amounted to average 70 min 8 min, in the group 2 (Omnopon in oberschwelliger dose) was the period 12 min 1.7 min, the animals, those superoxide and

Omnopon administered (group 3) already set after 6,1 min became 0.7 min their paw up and those the group 4 (H_2O_2 + Omnopon) already after 2,1 min 0.6 min.
[0054] Fig. 1: Effect of Trimeperimidin various dosage on pain sensitivity white rats in the Randall Selitto test.
Abscissa: Time after application (min)
Ordinate: Arbitrary units of the scaling of the Analgesimeters. The value 0 corresponds the determined basis IKD.
solid line: Control group
dotted line: Experimental group
Number of the animals: for each group n = 10
[estimates] $p < 0.05$; [estimates] [of estimates] $p < 0.01$
[0055] Fig. 2: Effect of immediate Trimeperimidin injected after inhalation of oxygen anion radicals (1 mg/kg) on pain sensitivity white rats in the Randall Selitto test.
Abscissa: Time after application (min)
Ordinate: Arbitrary units of the scaling of the Analgesimeters. The value 0 corresponds the determined basis IKD.
Number of the animals: for each group n = 16
[estimates] $p < 0.05$; [estimates] [of estimates] $p < 0.01$
[0056] Fig. 3: Effect of immediate Metamizol sodium of unterschwelliger dose (30 mg/kg), injected after inhalation of oxygen anion radicals, on pain sensitivity white rats in the Randall Selitto test.
Abscissa: Time after application (min)
Ordinate: Arbitrary units of the scaling of the Analgesimeters. The value 0 corresponds the determined basis IKD.
Number of the animals: for each group n = 10
[estimates] [of estimates] $p < 0.01$
[0057] Fig. 4: Effect from two hours to inhalation of oxygen anion radicals injected Trimeperimidin on pain sensitivity white rats in the Randall Selitto test.
Abscissa: Time after application (min)
Ordinate: Arbitrary units of the scaling of the Analgesimeters. The value 0 corresponds the determined basis IKD.
Number of the animals: for each group n = 8
[estimates] $p < 0.05$
[0058] Fig. 5: Influence of Nialamid (1 mg/kg) on the Trimeperimidin mediated Analgesie white rats in the edge all Selitto test 1 hour after the inhalation of oxygen anion radicals.
Abscissa: Time after application (min)
Ordinate: Arbitrary units of the scaling of the Analgesimeters. The value 0 corresponds the determined basis IKD.
Number of the animals: for each group n = 6
[estimates] $p < 0.05$
[0059] Fig. 6: Effect of Trimeperimidin (1 mg/kg) and Metamizol sodium (30 mg/kg) after intranasal injection of H_2O_2 on pain sensitivity white rats in the Randall Selitto test.
Abscissa: Time after application (min)

Ordinate: Arbitrary units of the scaling of the Analgesimeters. The value 0 corresponds the determined basis IKD.
Number of the animals: for each group n = 10
[estimates] $p < 0.05$
[0060] Fig. 7A: Effect of immediate morphine injected after inhalation of oxygen anion radicals (0.5 mg/kg) on pain sensitivity white rats in the Randall Selitto test.
Abscissa: Time after application (min)
Ordinate: Arbitrary units of the scaling of the Analgesimeters. The value 0 corresponds the determined basis IKD.
Number of the animals: n = see Tab. 1
[0061] Fig. 7B: Influence of Naloxon (0.5 mg/kg on morphine and/or superoxide-mediated Analgesie the white rats in the Randall Selitto test.
Abscissa: Time after application (min)
Ordinate: Arbitrary units of the scaling of the Analgesimeters. The value 0 corresponds the determined basis IKD.
Number of the animals: n = see Tab. 2

Claims:

1. Pharmaceutical agent to the treatment of pains, existing from a conventional analgesic, in particular an analgesic to the fight of potent pains, and oxygen anion radicals and/or their following and/or. Degradation products.
2. Pharmaceutical agent according to claim 1, characterised in that the analgesics of morphines, morphine of derivatives or morphine analogues is.
3. Pharmaceutical agent according to claim 1, characterised in that the analgesics not opioidartige compounds are.
4. Pharmaceutical agent after one of the preceding claims, characterised in that the oxygen anion radicals and/or their following and/or. Degradation products Perhydroxylradikale, hydrogen peroxide, other activated oxygen species or their hydrate cluster are.